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*Original Article*

# Evaluating the pharmacokinetic parameters of a single dose of oral disintegrating tablets in elderly patients with hypertension and hyperlipidemia

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**Abstract**

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, particularly in underprivileged areas such as Pakistan. Hypertension and hyperlipidemia are major risk factors for CVDs and often require medication for effective management. This study aimed to develop and validate a high-performance liquid chromatography (HPLC) method to assess the bioavailability of orally disintegrating tablets (ODTs) of atenolol and atorvastatin in elderly volunteers with high blood pressure and cholesterol levels by comparing the pharmacokinetic parameters of these ODTs with those of conventional tablet formulations. The study was conducted in Sargodha, Punjab Province, Pakistan, by recruiting 30 male and female elderly volunteers aged 45-65 years and weighing 60-90 kilograms. Each participant was administered a single dose of atenolol (25 mg), atorvastatin (10 mg), or an ODT containing both drugs. Blood samples were collected at specific intervals up to 48 hours postadministration. The concentrations of atenolol, atorvastatin, and the ODTs were measured using HPLC, and various pharmacokinetic parameters, including the area under the curve (AUC), maximum plasma concentration ($C_{max}$), and elimination half-life ($t_{½}$), were analyzed. The maximum concentration ($C_{max}$) of 10 mg atorvastatin occurred at 4 hours (9.50 ng/mL), while for 25 mg atenolol, it peaked at 4 hours (150.00 ng/mL). The ODTs showed comparable pharmacokinetic profiles, with the $C_{max}$ values for atorvastatin and atenolol at 4 hours being 4.00 ng/mL and 165.00 ng/mL, respectively. The elimination half-life ($t_{½}$) for the ODTs was 4.62 hours for atorvastatin and 4.95 hours for atenolol. The pharmacokinetic analysis indicated that the AUC and $C_{max}$ of the ODTs met the bioequivalence criteria, demonstrating absorption and elimination properties similar to those of conventional tablet formulations. The study concluded that the pharmacokinetic parameters of the ODT formulations atenolol and atorvastatin are comparable to those of conventional tablets. ODTs offer a viable and effective alternative for delivering these medications, particularly for patients who have difficulty swallowing pills, thereby potentially improving patient compliance.

**Keywords**

Orally disintegrating tablets; Chromatography, high-pressure liquid; Pharmacokinetic parameters; Hypertension; Hyperlipidemia; Cardiovascular diseases

## 1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, especially in underprivileged areas such as Pakistan [1,2,3]. The 20th century epidemiological shift has established CVDs as the leading cause of disability across the globe. While risk assessment methods exist for developed countries, no algorithm has been designed for low-

and middle-income populations [4,5]. CVDs are a significant health concern that can be influenced by certain risk factors. Hypertension (high blood pressure) and hyperlipidemia (high levels of cholesterol in the blood) are two major risk factors for CVDs. Additionally, diabetes is a threat to the elderly population. Unhealthy lifestyle factors such as high sodium intake, low potassium levels, and physical inactivity can increase CVD risk and are the main contributors to these diseases [6,7,8,9,10]. These risk factors can be managed through medications, surgical procedures, and lifestyle changes, including healthy diets, regular exercise, weight control, smoking cessation, and reduced salt and sugar intake [11,12,13].

Antihypertensive and lipid-lowering medications are often required as second-line treatments following nonpharmacological therapies, particularly for individuals at increased risk of CVDs [14,15,16,17]. Poor compliance with the prescribed treatment plan is a common issue in chronic conditions such as hypertension and dyslipidemia, which can worsen patient outcomes and increase mortality rates. This is often due to the complexity of drug regimens involving multiple tablets taken at different times [18,19,20]. The use of fixed-dose combination (FDC) tablets that contain both antihypertensive and lipid-lowering drugs can help healthcare providers address multiple CVD risk factors and improve patient adherence, leading to better therapeutic outcomes [21,22,23,24].

Melt-in-mouth or oral disintegrating tablets (ODTs) have become increasingly important, especially for patients who find it challenging to swallow traditional pills. This is particularly true for elderly and pediatric individuals [25,26]. These tablets are designed to dissolve quickly in the mouth, making them easier to administer and improving patient compliance [27,28,29]. Combination tablets containing aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins have been studied for preventing CVDs in high-risk individuals [30]. The primary objective of developing combination tablets is to enhance access to and adherence to multiple medications known to prevent recurrent myocardial infarction, stroke, and mortality, addressing gaps in CVD secondary prevention [31,32].

Researchers have studied ODTs for beta-blockers (atenolol) and statins (atorvastatin) to simplify drug regimens for elderly patients who are at risk of CVDs and to reduce missed doses [33,34]. Atenolol and atorvastatin are commonly used for the prevention of hypertension and hyperlipidemia, two conditions that frequently coexist and contribute to CVDs [25,26,35]. Studies have shown that combining antihypertensive treatments with HMG-CoA reductase inhibitors (such as atorvastatin) can efficiently reduce systolic and diastolic blood pressure, ultimately reducing mortality associated with CVDs [25,33,36].

The primary objective of this study was to assess the bioavailability of ODTs in elderly volunteers with high blood pressure and cholesterol levels using high-performance liquid chromatography (HPLC). Various pharmacokinetic parameters, such as the area under the curve (AUC), maximum plasma concentration ($C_{max}$), and elimination half-life ($t_{½}$), were assessed to optimize dosing and efficacy. This research provides insights into the use of ODTs as a convenient single-pill approach for preventing and managing CVDs.

## 2. Methods

The study was conducted in Sargodha, Punjab Province, Pakistan, and lasted six months from October 2022 to February 2023 after receiving approval from the Biosafety and Ethical Review Committee of the University of Sargodha (No. SU/BERC/147). This observational pharmacokinetic study compared the parameters of a single dose of atenolol, atorvastatin, and ODTs administered orally to male and female elderly volunteers aged 45-65 years and weighing 60-90 kilograms. Thirty volunteers who had already been prescribed atenolol and atorvastatin and were not on any other medication during

the study were recruited. Before the study, all participants were required to provide written consent to participate. The authors provided a clear explanation of the purpose of the study, its potential side effects, and the frequency of sampling. However, the study excluded those who did not consent to participate or who had multiple comorbidities [37].

### *2.1. Drug administration and blood sample collection*

The volunteers fasted overnight, and blood samples were collected before administering the drug. Control samples were collected prior to administration [37].

#### 2.1.1. Atenolol administration and sampling

After a two-hour break following the meal, the participants were administered a single dose of atenolol (tenormin 25 mg, Abbott, Karachi, Pakistan). Blood samples were taken at specific time intervals of 1, 2, 4, 6, 8, 10, 12, 24, and 48 hours after administering the dose. The samples were stored in centrifuge tubes containing heparin at 37°C. The pH of the samples was maintained using a Beckman HS (Germany) electric pH meter. For further separation of the plasma, the samples were centrifuged for 20 minutes at 4000 rpm and then stored at -20°C [38].

#### 2.1.2. Atorvastatin administration and sampling

After a two-hour delay from the meal, the volunteers were given a dose of atorvastatin (Atorva 10 mg, Pharmatec Pakistan (Pvt) Ltd.). Blood samples were collected at 1, 2, 4, 6, 8, 10, 12, 24, and 48 hours using heparinized centrifuge tubes. The pH of the samples was maintained using a Beckman HS (Germany) electric pH meter at 37°C. For further separation of the plasma, the samples were centrifuged for 20 minutes at 4000 rpm and then stored at -20°C [38].

#### 2.1.3. ODT administration and sampling

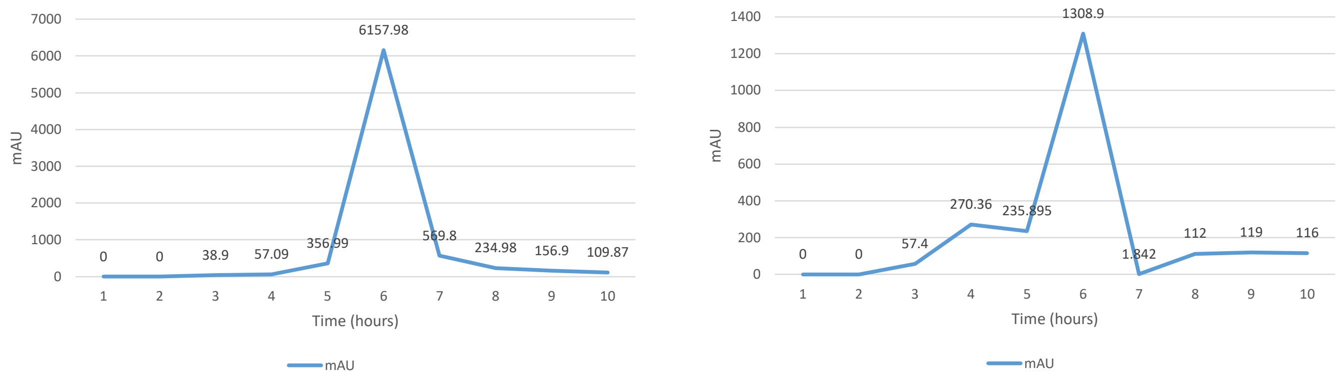
After a two-hour meal break, the participants were given a single dose of ODTs. Blood samples were collected in heparinized plastic centrifuge tubes at 1, 2, 4, 6, 8, 10, 12, 24, and 48-hour intervals. The pH of the samples was maintained using a Beckman HS (Germany) electric pH meter at 37°C. For further separation of the plasma, the samples were centrifuged for 20 minutes at 4000 rpm and then stored at -20°C [38].

### *2.2. Analytical methods*

The atenolol, atorvastatin, and ODT levels in the collected samples were measured using HPLC (Agilent 1200 series). The measurements were taken using a Shim-Pak ODS column with dimensions of 5 µm (4.6 X 250 mm) at a flow rate of 1.0 mL/min regulated by a solvent delivery system. The effluent from the column was detected using a fluorescence detector set at an excitation wavelength of 228 nm [37,39].

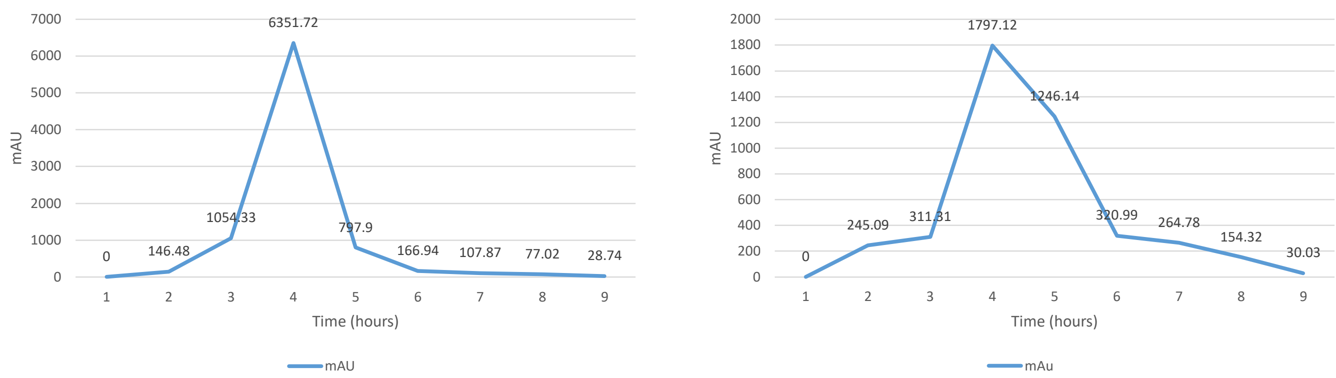
### *2.3. Chromatographic conditions*

The samples were analyzed using a mobile phase of acetonitrile and methanol at a 30:70 ratio to determine the concentrations of atenolol, atorvastatin, and ODTs. The pH was adjusted to 3.7 by adding orthophosphoric acid. A UV–visible detector with a wavelength of 300 nm and an injection volume of 20 µL was used, and the temperature was maintained at 30°C during chromatographic analysis [37,40].



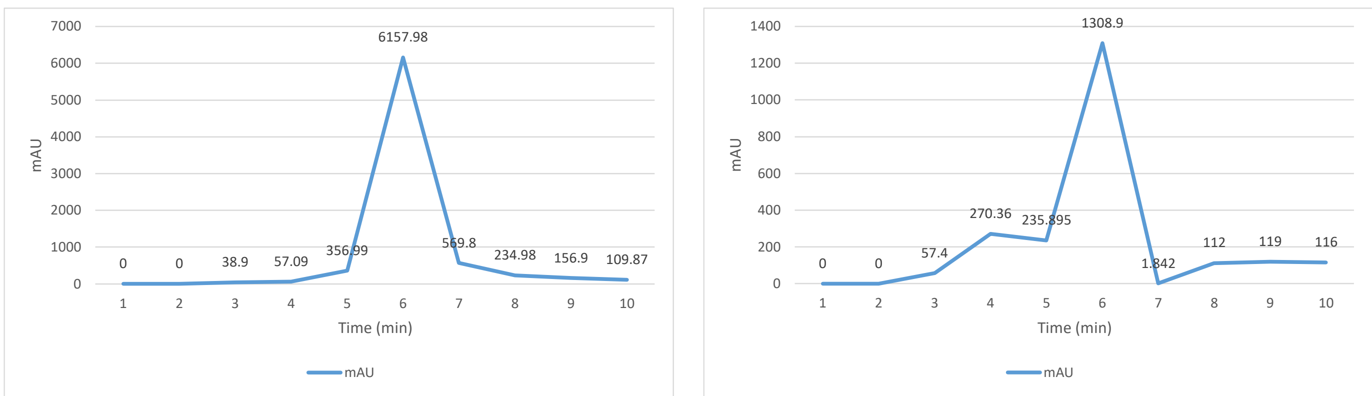

(**a**) (**b**)

**Figure 1.** (**a**) Atorvastatin concentration of 0.01 mg/mL in plasma; (**b**) Plasma atorvastatin standard drug.




(**a**) (**b**)

**Figure 2.** (**a**) Atenolol concentration of 0.01 mg/mL in plasma; (**b**) Atenolol standard drug in plasma.




(**a**) (**b**)

**Figure 3.** (**a**) ODT standard drug in plasma; (**b**) ODT 0.01 mg/mL concentration in plasma.

*2.4. Standard solutions and standard curve preparation*

To prepare the standard stock solutions of atenolol, atorvastatin, and ODTs, 100 mg of each drug was dissolved separately in 100 mL of solvent in a calibrated flask, creating a 1 mg/mL drug solution for each standard stock solution. Each solution was then diluted 10 times to obtain a 0.1 mg/mL concentration, and the pH was adjusted to 4 using orthophosphoric acid. Figures 1a, 1b, 2a, 2b, 3a, and 3b show the calibration curves, which plot the peak area data against the corresponding concentrations.

*2.5. Sample preparation*

To prepare each plasma sample (250 µL) for analysis, it was transferred to a 2 mL polyethylene vial and centrifuged. A 2 mL glass vial was used for the collection of the organic layer, and at 40°C, nitrogen gas was used to evaporate the solvent to leave a dry residue. Next, 250 µL of the mobile phase was added to reconstitute the remaining material. For analysis, twenty microliters of the reconstituted solution was administered and injected into the chromatographic column, and this process was repeated for each sample [38].

*2.6. Determination of drug concentrations in volunteer plasma*

A reference solution was used to compare the peak areas of atenolol, atorvastatin, and ODTs and determine their respective concentrations in plasma samples. The equation Y = a + bx was utilized to determine the drug concentration. In this equation, Y characterizes the peaks of the unknown sample, a represents the intercept, b indicates the slope of the regression line, and x denotes each drug concentration.

*2.7. Calculations and statistical analysis*

The data are presented as the means and standard deviations. The changes in the plasma concentration over time were determined using a two-compartment open model, and graphs were created. Descriptive statistics were used to compare the pharmacokinetic parameters of atenolol, atorvastatin, and the ODTs. The pharmacokinetic parameters were used to determine the most effective way to administer a single ODT compared to standard atenolol and atorvastatin in the participants [37,41].

## 3. Results

*3.1. Plasma concentrations of atorvastatin, atenolol, and ODTS in participants*

Table 1 presents the average plasma concentrations of 10 mg atorvastatin, 25 mg atenolol, and ODTs (atenolol + atorvastatin) over time in the participants. For atorvastatin, the maximum concentration ($C_{max}$) of 10 mg occurred at 4 hours, reaching 9.50 ng/mL, and gradually decreased to 2.00 ng/mL at 24 hours. Similarly, the pharmacokinetic parameters of 25 mg atenolol were 45.00 ng/mL at 1 hour, with the maximum concentration at 4 hours reaching 150.00 ng/mL and decreasing to 25.00 ng/mL at 24 hours. For the ODTs, the average concentration of atorvastatin at 1 hour was 0.50 ng/mL, with a maximum concentration of 4.00 ng/mL at 4 hours, and the concentration decreased to 1.00 ng/mL at 24 hours. The atenolol component of the ODTs showed similar trends, with the average concentration matching the standalone atenolol results at the corresponding time points.

**Table 1.** Plasma concentrations vs. time for atorvastatin, atenolol, and ODTs.

| Time (Hour) | Atorvastatin 10 mg Average Concentration (ng/mL) | Atenolol 25 mg Average Concentration (ng/mL) | Atorvastatin 10 mg Average Concentration (ng/mL) |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | Mean ± SD |
| 0 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 |
| 1 | 3.00 ± 0.155 | 45.00 ± 0.718 | 0.50 ± 0.120 |
| 2 | 8.00 ± 0.844 | 130.00 ± 0.508 | 0.75 ± 0.050 |
| 4 | 9.50 ± 0.722 | 150.00 ± 0.643 | 4.00 ± 0.022 |
| 6 | 7.50 ± 0.528 | 110.00 ± 0.691 | 2.30 ± 0.041 |
| 8 | 5.50 ± 0.565 | 90.00 ± 0.714 | 1.37 ± 0.106 |
| 10 | 4.00 ± 0.364 | 88.00 ± 0.727 | 1.35 ± 0.009 |
| 12 | 3.20 ± 0.104 | 87.00 ± 0.547 | 1.31 ± 0.005 |
| 24 | 2.00 ± 0.077 | 25.00 ± 0.730 | 1.00 ± 0.005 |

### *3.2. Pharmacokinetic parameters*

The pharmacokinetic analysis was carried out using a method that does not rely on a specific model. The $C_{max}$ (maximum concentration in plasma) and $t_{max}$ (corresponding peak times) of atenolol, atorvastatin, and the ODTs were measured by evaluating the plasma concentration-time profiles of the individual drugs. The $K_e$ (elimination rate constant) values were obtained by fitting a least squares regression to the terminal log-linear portion of the plasma concentration profile. The elimination half-life ($t_{½}$) was calculated as 0.693/$K_e$. The trapezoidal rule was used to estimate the AUC until the last measurable concentration (AUC $_{0\text{-}t}$) was reached. The AUC extrapolated to infinity (AUC $_{0\text{-}\infty}$) was determined. The pharmacokinetic analysis regarded the AUC $_{0\text{-}t}$, AUC $_{0\text{-}\infty}$, and $C_{max}$ as the primary variables.

Table 2 shows the mean concentration-time profiles of 10 mg atorvastatin, 25 mg atenolol, and the ODTs after oral administration. For atorvastatin, the $C_{max}$ was 13.70 ng/mL at approximately 2.99 hours, with an elimination half-life ($t_{½}$) of 6.93 hours, indicating that it is well suited for single dosing. The $K_e$ was 0.1. Atenolol (25 mg) had a $C_{max}$ of 177.00 ng/mL at approximately 2.97 hours, with an elimination half-life ($t_{½}$) of 5.77 hours, which is also suitable for single dosing. For the ODTs, the $C_{max}$ values for atorvastatin and atenolol were 5.00 ng/mL and 165 ng/mL, respectively, with $t_{max}$ values of 3.03 hours and 2.71 hours, respectively. The $t_{½}$ values for the ODTs were 4.62 hours for atorvastatin and 4.95 hours for atenolol, indicating that the ODT formulation provides a pharmacokinetic profile similar to that of the individual drugs. The $K_e$ values were 0.15 and 0.14, respectively.

**Table 2.** Pharmacokinetic evaluation of atenolol, atorvastatin, and the ODTs.

| Pharmacokinetic Parameter | Atorvastatin (10 mg) | Atenolol (25 mg) | ODTs (Atenolol) | ODTs (Atorvastatin) |
|---|---|---|---|---|
| AUC $_{0\text{-}24}$ (ng.h/mL) | 903.00 | 1352.00 | 1236.00 | 23.79 |
| AUC $_{0\text{-}\infty}$ (ng.h/mL) | 88.30 | 11475.00 | 10693.00 | 43.06 |
| $C_{max}$ (ng/mL) | 13.70 | 177.00 | 165.00 | 5.00 |
| $t_{max}$ (h) | 2.95 | 2.97 | 2.71 | 3.03 |
| $t_{1/2}$ (h) | 6.93 | 5.77 | 4.62 | 4.95 |
| $K_e$ ($h^{-1}$) | 0.10 | 0.12 | 0.15 | 0.14 |

## 4. Discussion

An ODT is a better mode of delivery for patients who have difficulty swallowing pills. Compared with conventional tablets, ODTs are more accessible to administer, cause less

physiological stress, and improve patient compliance [42]. In a study of elderly patients, more than half preferred ODTs over conventional tablets due to their ease of use [28]. Hypertension and hyperlipidemia are risk factors that contribute to CVD. Poor lifestyle habits, inappropriate diet, and fast food consumption in Asian communities increase the likelihood of developing CVD. While providing adequate treatment is essential, improving adherence to and control of these diseases is crucial. Atenolol (tenormin) and atorvastatin (Atorva) are commonly used and effective treatments in traditional tablet form. This study showed that a single dose of an ODT formulation (atenolol or atorvastatin) with or without water has the same profile as a conventional tablet [43].

This study aimed to compare the pharmacokinetic properties of a new single-dose formulation of ODTs (atenolol + atorvastatin) with those of conventional atorvastatin (10 mg) and atenolol (25 mg) formulations. The results demonstrated that the AUC and $C_{max}$ met the bioequivalence criteria [43]. Atenolol and atorvastatin (ODTs) have been developed as alternative dosage forms for patients who have difficulty swallowing or who are complying with their medication. These ODT tablets dissolve quickly in the mouth, allowing easy swallowing without the need for water [44]. Bioequivalence studies have confirmed that the $C_{max}$ and AUC of ODTs are equivalent to those of conventional tablets of atenolol and atorvastatin. Therefore, ODTs can be considered clinically interchangeable with tenormin (25 mg) and atorva (10 mg).

Studies on pharmacokinetic data have shown that ODTs have absorption characteristics almost equivalent to those of conventional commercial tablets. ODTs promote quicker drug absorption when drug dissolution begins in the buccal cavity [44]. This, in turn, enhances bioavailability compared to conventional tablets, as ODTs are expected to bypass first-pass metabolism [45]. Volunteers who were administered individual tablets of atenolol and atorvastatin exhibited ODT oral absorption after administration, with a median time to maximum concentration ($t_{max}$) of approximately 3-4 hours.

Furthermore, buccal cavity absorption also affects the physicochemical properties of the material. The formulation of ODT tablets is designed to rapidly disintegrate (within 30 seconds) upon contact with saliva when placed on the tongue. Disintegrated tablets have a limited contact time of less than a minute, making them unsuitable for buccal absorption, even when administered with water [44,46,47]. The elimination half-life ($t_{½}$) values of the ODTs and conventional separate tablets of atenolol and atorvastatin were compared. Both have a $t_{½}$ of approximately 24–48 hours. A single dose of either is enough to achieve efficacy in targeting hypertension and hyperlipidemia [44].

Atenolol and atorvastatin are drugs used to treat various heart conditions and have well-established safety and efficacy profiles. In addition to conventional tablets, a new ODT containing both drugs is now available. This tablet provides a discreet and convenient option for patients with dysphagia to take medication without water. The ODT formulation is advantageous because it offers quick absorption and fast relief for patients. However, the studies conducted on these drugs were limited to a particular age group with selective issues that increased the risk of CVD. Therefore, the present study lacked results for patients receiving other medications. Further research can emphasize this aspect by administering ODTs to patients taking more medication and observing the bioavailability of the drug.

One limitation of this study is the lack of formal inferential statistical tests to compare the pharmacokinetic parameters between different formulations. Additionally, the study was limited to a specific age group and did not account for the effects of other medications the participants might have been taking. Future studies should include broader demographic information and consider the impact of concomitant medications on the pharmacokinetic profiles of ODTs.

## 5. Conclusions

The study concluded that the absorption and elimination properties and behaviors of the individual drugs atenolol and atorvastatin remained consistent even with increasing drug concentration. The pharmacokinetic parameters of the ODT formulations were comparable to those of the standard drug formulations. Therefore, ODTs containing both atenolol and atorvastatin exhibit the same pharmacokinetic properties as the individual drugs when administered alone. This suggests that ODTs are a viable and effective alternative to conventional tablets for delivering these medications, offering an option that may improve patient compliance, particularly for those who have difficulty swallowing pills.

**Author contributions:** Conceptualization, KK, HI, and SF; methodology, KK, HI, and SF; software, KK; validation, KK; formal analysis, KK; investigation, KK, HI, and SF; resources, KK; data curation, KK; writing—original draft preparation, KK, HI, and SF; writing—review and editing, KK; visualization, KK; supervision, KK; project administration, KK, and SF. All authors have read and agreed to the published version of the manuscript.

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**Ethics statement:** The study received ethics approval from the Biosafety and Ethical Review Committee of the University of Sargodha (No. SU/BERC/147).

**Consent to participate:** Written informed consent was obtained from all participants prior to data collection.

**Data availability:** The data supporting this study's findings are available from the corresponding author, Khushbu, upon reasonable request.

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**Conflicts of interest:** The authors declare no conflicts of interest.

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